Pharmacology of Atherosclerosis

Introduction

Recall from the last lesson that the problem was circulating LDL being deposited into weakened endothelium. Familial mutations in the LDL receptor, which prevents LDL from exiting the circulation, cause atherosclerotic disease in patients in their 20s, whereas atherosclerotic disease usually occurs in patients in their 60s or older. Therefore, the problem is LDL. With that perspective, the natural conclusion is that the treatment of atherosclerosis should be to reduce LDL levels. And that's true, but only sort of true. As we will see, the most effective therapies to treat atherosclerosis **increase LDL receptor expression** in the hepatocytes.

The life cycle of cholesterol and lipoproteins is discussed in detail in Metabolism #14: *Triglyceride Mobilization*. The salient points are included here to orient us for this pharmacology lesson.

The **liver** synthesizes 70% of the body's cholesterol. The liver synthesizes **VLDL** (very-low-density lipoproteins), rich in lipids and cholesterol, and releases them into the bloodstream. There, the VLDL particles are activated by high-density lipoproteins (HDL) to acquire the apoproteins necessary for recognition by peripheral tissues. The peripheral tissues take the lipids and cholesterol from the VLDL, resulting in intermediate-density lipoprotein (IDL) particles, which we refer to as "VLDL remnants" (because they behave almost identically to chylomicrons, below). HDL adds cholesterol from the periphery to the IDL, turning it into low-density lipoprotein (LDL). LDL then returns to the liver. If the LDL particle receives the liver's signal to "come on home out of the rain" via **LDL receptor** expression, then the LDL particle exits circulation into the liver. If it doesn't receive the "come home" signal, the LDL particle is forced to endure a lonely cycle around the bloodstream, homeless and alone. Every time the LDL particle comes close to the liver, it checks for the LDL receptor. If it finds one, it gets to come inside. If it doesn't, back out into the world (circulation) it goes. **Chylomicrons** from the diet are analogous to the VLDL particles—they are packed with cholesterol and fatty acids, head to the periphery, and then come to the liver for processing.

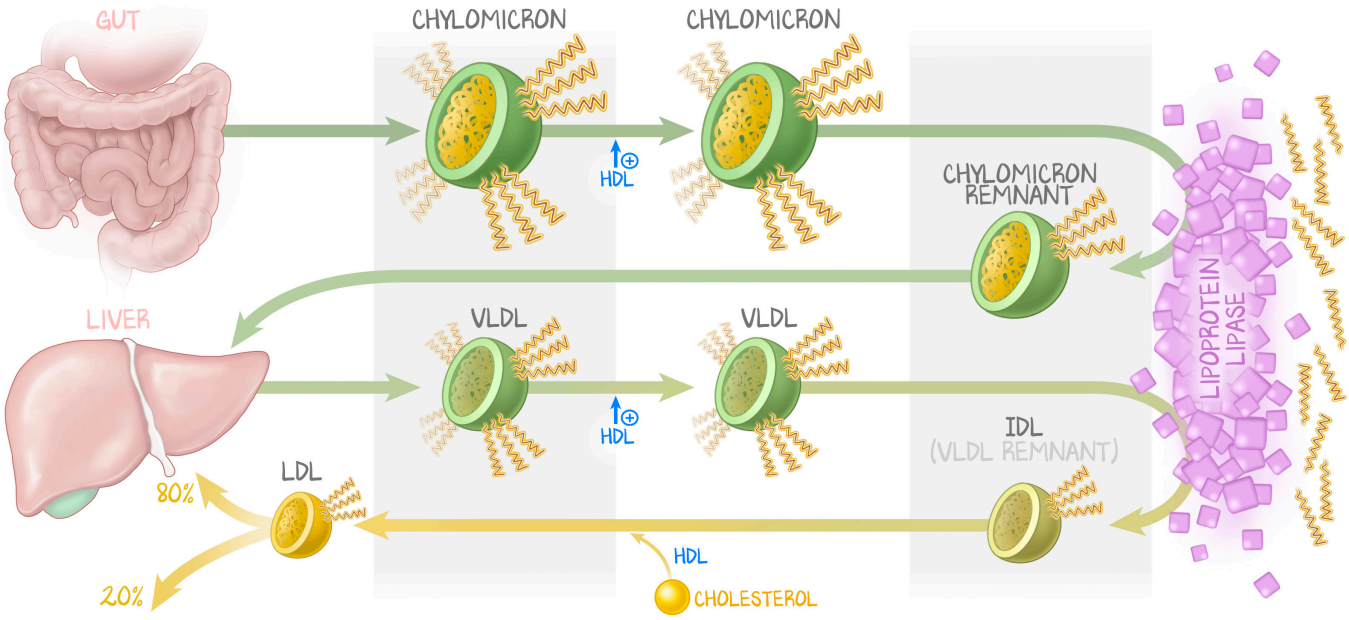

Figure 2.1: Overview of the Cholesterol Pathways
This illustration is a call back to Biochemistry with some of the details removed (specifically, apoprotein details). This is to remind you that cholesterol enters the body from the diet as chylomicrons, which serve a similar purpose to and share a similar shape with the VLDL particles. Both chylomicrons and VLDL are activated by HDL, deliver cholesterol and fatty acids to the periphery via endothelial cells' lipoprotein lipase, and then head to the liver.. The difference between them is thet chylomicron remnants always get into the liver for processing—LDL has to be let in. The IDL, analogous to the chylomicron remnant has peripheral cholesterol added to it by HDL, making LDL. LDL then returns to the liver or circulates. In a cholesterol deficient state (most of mankind's existence except for the past hundred years) 80% of circulating LDL is brought home by the liver. Now in a time of calorie excess and cholesterol abundance, that ratio is reduced—most LDL stays in circulation.

The liver can choose what to do—synthesize new lipoproteins and cholesterols from scratch, use the stuff coming in from the diet, or recycle the ones in circulation. Until very recently in human evolution, food was not abundant. Cholesterol is essential for normal cell function—for every cell membrane and every membrane of every organelle. Having circulating LDL meant there was enough cholesterol to go around for all the cells. It also served as a reservoir for the liver to grab hold of if there wasn't enough material coming from the diet. Now that we have abundant access to food, LDL accumulates in the bloodstream because the liver has little need to pull it out of circulation. And the default function of the liver is to ignore circulating LDL because it might need it later. It always uses new cholesterol from the diet first, builds new cholesterol second, and only calls on that guaranteed reservoir last.

If we have an abundance of cholesterol in our diet, then the chylomicrons keep pouring into the liver. The liver recycles those chylomicrons into VLDL particles, which eventually become LDL particles. The liver, having an abundance of chylomicrons feeding it cholesterol and VLDL parts, never needs to pull the LDL particles from circulation. This means that the liver keeps using chylomicron remnants to make more VLDL and, therefore, more LDL and doesn't pull any of the pre-existing LDL out of circulation. The cycle repeats on and on, and LDL accumulates in the bloodstream.

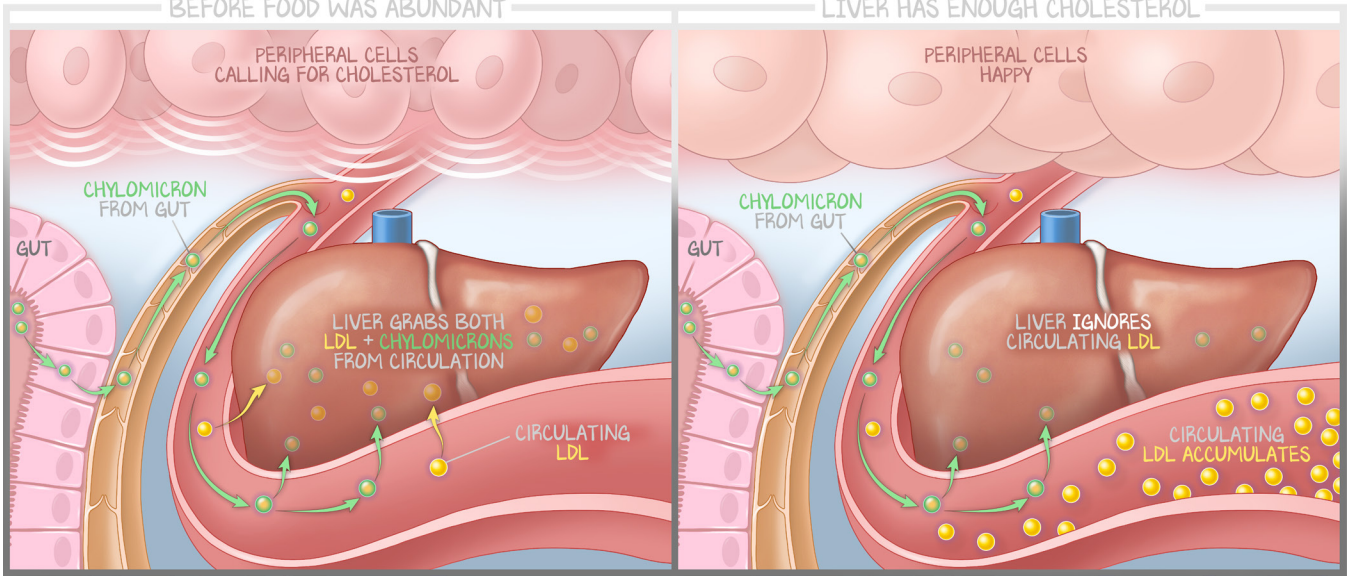

Figure 2.2: The Story of How and Why LDL Accumulates
It all has to do with whether the liver has enough cholesterol. LDL is actually a reservoir of useful cholesterol. But the accumulation of too much can be bad. It is up to the liver to bring the LDL home or continue to use chylomicrons. When food was scarce, the liver had to use its precious reserve of cholesterol—circulating LDL—to deliver enough cholesterol to the peripheral tissues. Now that food is abundant, the liver behaves as evolution has informed it to—use what is coming in from the diet and allow the precious circulating cholesterol (as LDL) to accumulate. We never needed a sensor for excess LDL (because it was a scarce resource), so humans don't have one, nor do we have any mechanism for eliminating LDL. Therefore, LDL accumulates in the blood.

All LDL wants to do is come home, unload its cargo, and get out of circulation. Every time LDL comes by the house, it looks for the sign that it's okay to come in. There's no sign. Every time. LDL can only take so much, try so many times to come home, before giving up. After a while of trying to come back home, watching chylomicrons coming and going day after day, the homeless LDL gives up. LDL just drives around, looking for a place to sleep. And the first easy turn off the highway of life will do. Where does that LDL end up? Under a bridge. Living in a van, down by the river *(this may be an esoteric reference for many readers, but it's still one of the best SNL skits ever)*. Turns out there are other homeless, disgruntled LDLs already there. This new LDL joins the band of merry disgruntled homeless LDLs shunned by the liver. And now they have a new home. Together. And they ain't leaving.

The "come home" signal is the LDL receptor. The LDL is circulating LDL. The easiest way out of the bloodstream is through a dysfunctional endothelium. And the band of homeless LDLs living together is the fatty streak.

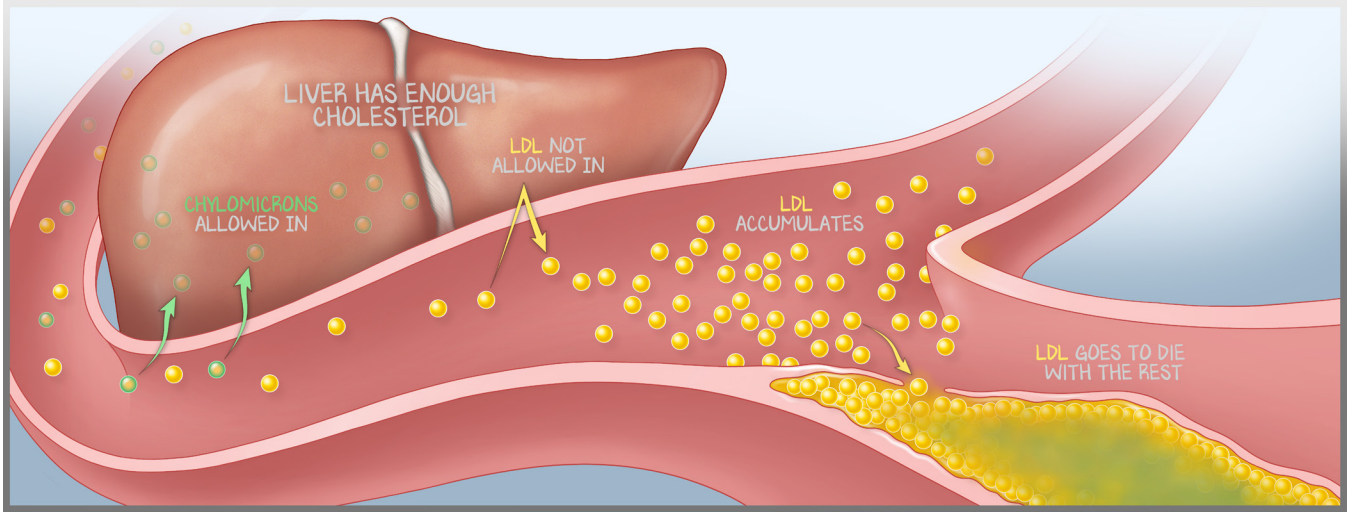

Figure 2.3: The Story of LDL Deposition
When the liver has enough cholesterol, it doesn't invite the LDL back in, and the LDL accumulates. Despondent LDLs go to atherosclerotic plaques to die in the lipid core when they get tired of waiting to be let into the liver.

The goal of pharmacology for the treatment of atherosclerosis is to help the liver realize its mistake—to let the LDLs come home again. To pull LDLs from circulation so that they stop ending up in suicide colonies of sad, homeless LDLs in atherosclerotic plaques. **The goal of atherosclerosis treatment is to increase LDL receptor expression on the hepatocytes.** Because the liver can use new chylomicrons from the diet, synthesize new cholesterol from constituent parts, or bring in circulating LDL, the targets of therapy are to reduce incoming cholesterol via chylomicrons, inhibit the production of new cholesterol, and maintain the LDL receptor population on hepatocytes. Although lipoprotein lipase is relevant to the biochemistry of lipid metabolism, it isn't relevant in any way to the management of atherosclerosis.

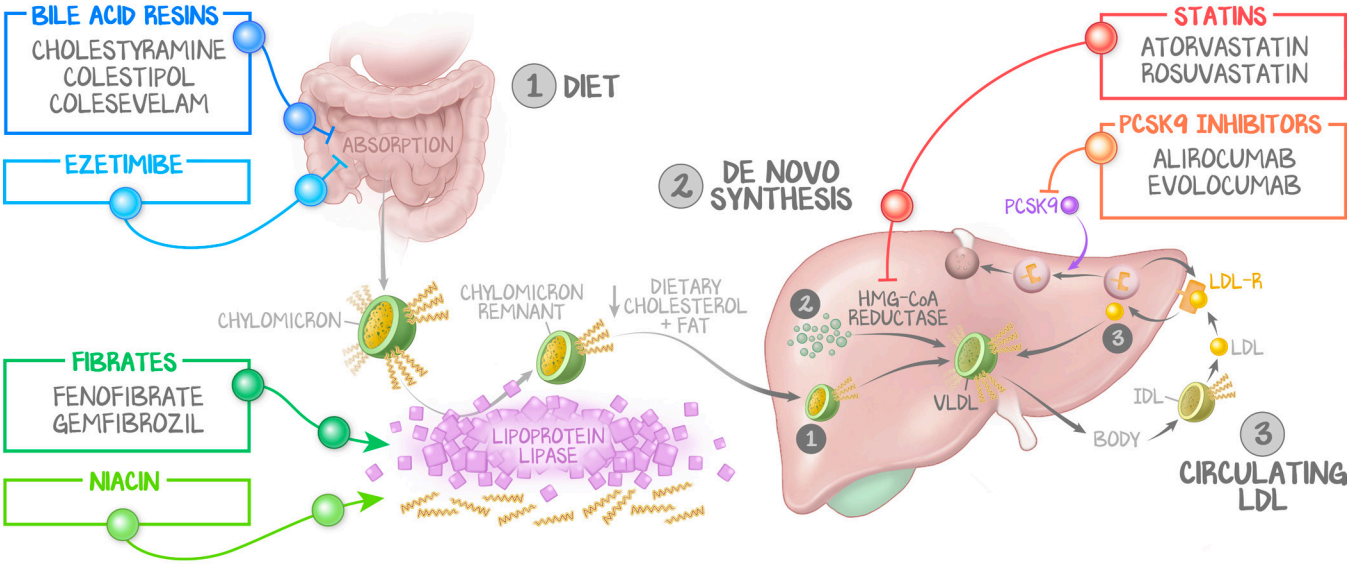

Figure 2.4: Targets of Lipid Therapy
Statins inhibit the synthesis of new cholesterol by increasing LDL receptor expression so that the liver uses circulating LDL as well as dietary cholesterol. PCSK9 inhibitors inhibit the degradation of LDL receptors so that the liver keeps using circulating LDL as well as dietary cholesterol instead of making more. Gut-active medications prevent dietary cholesterol from being absorbed so that the liver uses more circulating LDL ~~by increasing LDL receptor expression~~. Oh, wait. Niacin and fibrates have nothing to do with LDL receptor expression and were, but no longer are (at least, not as it relates to atherosclerosis), used to treat lipid disease.

Statins

Statins are HMG-CoA reductase inhibitors. They inhibit the rate-limiting step of cholesterol synthesis in the hepatocytes. The chylomicron supply of cholesterol and lipoprotein is not enough for the liver to keep up the production of VLDL. It would make sense that, by inhibiting the liver's ability to synthesize cholesterol from constituent parts, there would be less VLDL made and, therefore, less LDL circulating. But the reduced cholesterol production is not why statins work so well. The liver is reminded of the vast supply of accumulated cholesterol riding around on LDL. The reduced cholesterol production leads to **upregulation of LDL receptors** in order to use the cholesterol stored on LDL. Now when LDL comes around the liver, the "come home" signal is up, and the LDL exits the circulation. LDL, no longer homeless and alone, doesn't go searching for the atheromas full of other disgruntled LDLs to hang out with. Atherosclerosis is slowed. LDL levels fall.

Statins are the **best pharmacological treatment for atherosclerosis**. Why? Because they get LDL out of the circulation. Statins are discussed in detail in CAD #4: *Chronic Ischemic Heart Disease Pharmacology*.

PCSK9 Inhibitors

PCSK9 inhibitors are **injectable monoclonal antibody** medications. PCSK9 is an enzyme that degrades LDL receptors. When the LDL receptor binds LDL, it is internalized by endocytosis. The LDL receptor is either degraded in a lysosome or recycled to the plasma membrane. If PCSK9 is present, the LDL receptor is degraded. If it's not present, the LDL receptor is recycled. PCSK9 inhibitors increase LDL receptors by preventing their destruction. Statins increase LDL receptors by inducing more to be made. The same effect is achieved—more LDL receptors = less circulating LDL. PCSK9 inhibitors are used in patients who cannot tolerate a statin and those who experience vascular events while on maximum statin therapy. They are inconvenient, being injectable, but they are just as good as statins at lowering circulating LDL and treating atherosclerosis. Their names are alirocumab and evolocumab. Like all monoclonal antibodies, they end in -mab; that suffix does not indicate that their target is PCSK9, only that they are monoclonal antibodies. They also seem to cause muscle-related complaints, but to a lesser extent than statins. Their main side effects are **flu-like symptoms** (they are antibodies) and **inflammation at the injection site**.

Bile Acid Resins

The only way cholesterol leaves the body is through bile acids. The liver synthesizes bile acids from cholesterol. Bile acids are supposed to help degrade food and emulsify fats and then re-enter the system in chylomicrons. They are secreted into the gut and reabsorbed from the gut in what is called **enterohepatic recirculation**. By ingesting a bile acid resin into their gut lumen, the patient prevents this enterohepatic recirculation. This has a double effect—cholesterol (in the form of bile acids) is eliminated in the stool, AND new fats aren't absorbed. That means the liver has to make new bile acids, which it uses cholesterol to do. That also means that new cholesterol and lipids aren't coming from the diet as chylomicrons. This means that, ultimately, the liver **upregulates LDL receptors** to pull more LDL from the circulation. That sounds like the effect of statins.

The positive atherosclerotic effects of bile acid resins are similar to those of statins . . . if patients actually take them. But bile acid resins are just aren't as practical as statins because of their side effects.

Not absorbing fats and cholesterol from your gut means osmotically active compounds remain in your gut. This pulls water from your body, resulting in steatorrhea and diarrhea. Not absorbing fats means **fat-soluble vitamins** (ADEK) don't get absorbed, resulting in deficiency. None of the fat calories consumed can get used by the body. All of this is just another way of saying "malabsorption syndrome." Taking a bile acid resin with warfarin, a vitamin K epoxide inhibitor, may lead to excess anticoagulation

due to the loss of vitamin K. Bloating is uncomfortable. And **fatty stool smells awful**. And this is what causes most bile acid resin noncompliance—uncomfortable tummies and foul stool from steatorrhea. Oh, and remember General Pharmacology #2: *Absorption*, how we manufactured drugs to get into our bloodstream? Make them small and lipophilic. If you block fat absorption, you can also compromise the absorption of many drugs.

Drug names in this class are **chole**styramine, **cole**stipol, and **cole**sevelam. The chole/cole prefix alludes to the fact that bile acids are stored in the gallbladder, where gallstones can form, called chole lithiasis. Chole is for gallbladder, not cholesterol. They would work, but, considering their terrible side effects, **dietary restriction of cholesterol** is superior.

Cholesterol Absorption Inhibitor = Ezetimibe = Diarrhea

Knowing that bile acid resins have a statin-like effect on LDL receptors and LDL levels but that malabsorption syndromes are not a good thing to induce in patients, another intestinal blocker, **ezetimibe**, was made. It doesn't bind up bile acids like bile acid resins do, losing the cholesterol from the bile acids along with the dietary fat. Instead, it goes after the cholesterol directly. It has the same idea as bile acid resins—go after the cholesterol before it gets into the body—but with an attempt at side effect reduction—don't cause severe fat malabsorption syndromes.

The malabsorption syndromes from ezetimibe aren't as severe as with bile acid resins, but **diarrhea** and **steatorrhea** make the drug a no-go for most patients. It does work. It just has bad GI side effects that make it not worth it. And the outcome is something like you'd expect. Because the malabsorption isn't as bad, the diarrhea isn't as bad, but the LDL reduction isn't as good. So . . . a drug that doesn't work as well but still causes diarrhea and steatorrhea means that ezetimibe, like its bile acid resin cousins, is a no-go drug.

Fibrates

Fibrates are used to treat hypertriglyceridemia. They are not used to treat LDL, and they are not used to treat atherosclerosis. They are included here because, until around 2012, they were THE OTHER DEFINITIVE treatment next to statins. Now that medical science has such a better understanding of LDL and the LDL receptor, they are obviously not useful in the treatment of LDL.

Lipoprotein lipase is an enzyme found on endothelial cells, particularly those of skeletal muscle, and adipocytes. Lipoprotein lipase cleaves fatty acids from circulating VLDL particles, making IDL from VLDL. If you're a skeletal muscle myocyte, that liberated fatty acid can be used as a fuel source. Adipocytes use those free fatty acids from triglycerides during the insulin-dominant state so they can release them back to the liver during the glucagon-dominant state. Endothelial cells express more lipoprotein lipase when the nuclear transcription factor receptor **PPAR-α** (pronounced "pee-par-alpha") is bound to its ligand. Fibrates act as ligands for PPAR-α.

Hepatocytes express LDL receptors and have HMG-CoA synthase. Statins inhibit HMG-CoA synthase, thereby increasing LDL receptor expression, thereby pulling LDL out of circulation. Endothelial cells express lipoprotein lipase, an enzyme that cleaves fatty acids from VLDL so that adipocytes can store the free fatty acids as triglycerides. **Fibrates activate PPAR-α in endothelial cells**, pulling fatty acids out of circulation, thereby reducing the triglyceride content of the blood.

Think about what this drug is doing. It is reducing the amount of triglyceride in the blood by shifting it to tissues. The **serum triglycerides plummet**. But the body triglycerides don't change—the serum levels do. This is useless for atherosclerosis. It doesn't affect LDL levels or LDL receptor expression. It

is only useful for patients with **excruciatingly high serum triglycerides** (familial hypertriglyceridemia) who end up with complications, such as pancreatitis, due to triglyceride levels in the thousands. Their issue isn't an abundance of LDL or cholesterol but rather a genetic defect that prevents the clearing of triglycerides from the blood. The triglycerides cause disease, and that disease is not atherosclerosis.

Fenofibrate and **gemfibrozil** are common fibrates. Fibrates can result in **myopathy** and cause a **synergistic** increase in the risk of myopathy if coadministered with a statin. They can also cause cholesterol gallstones. Fibrates lower triglyceride levels. They don't let the LDL come home. There is no change in LDL receptor expression. Fibrates just hide the triglycerides in tissues. Don't treat atherosclerosis due to dyslipidemia (LDL problems) with fibrates. **Do treat hypertriglyceridemia with fibrates.**

Niacin

Fibrates force more triglycerides to be stored in adipocytes. Niacin makes sure those triglycerides **stay** in the adipocytes. Niacin **inhibits hormone-sensitive lipase** in adipose tissue, preventing the release of fatty acids into the bloodstream. When in the glucagon-dominant state, between meals, the release of fatty acids into the blood stream are how the liver gets the energy stored in those fatty acids that were dispatched for storage in the adipose back.. Niacin also **raises the HDL** by almost 30%, making it the most effective HDL-raising medication.

Notice how we didn't say "good cholesterol" or "bad cholesterol" in this lesson. The goal of treating atherosclerosis is about giving circulating LDLs a home to come to in the liver. Having more HDL doesn't make you better or reduce the risk of disease. That was something medical science believed at one point in time: HDL good, LDL bad. NO. A small fraction of lipid and cholesterol is returned to the liver directly by HDL. HDL "returns cholesterol from the periphery" by taking it from dead cells or artery walls and **giving it to IDL**, which **makes LDL**, and LDL is the one that brings it back to the liver. We used to think that having a higher HDL could cancel the negative effects of a high LDL. Wrong. Oh, and niacin causes hyperglycemia (diabetes) and hyperuricemia (gout) and is hepatotoxic. Don't use niacin to treat anything lipid related.

Niacin is still relevant in pharmacology because of its side effect: **flushing**. Flushing that can be prophylaxed against using **aspirin**. That obvious-side-effect-with-an-obvious-antidote remains a fun factoid for question writers to amuse themselves with. Nothing more. Never choose niacin as an intervention.

CLASS	MECHANISM	DOWNSTREAM EFFECT
Statins	HMG-CoA reductase inhibitor Endogenous cholesterol synthesis inhibited (no cholesterol synthesized)	Increased LDL receptor expression Clears LDL from circulation
Bile acid resins *Cholestyramine* *Colestipol* *Colesevelam*	Bind to bile acids in the intestine, prevent recirculation of bile acids, prevent cholesterol and lipid absorption in the gut (no dietary cholesterol)	Increased LDL receptor expression Clears LDL from circulation Causes malabsorption Vitamin ADEK deficiency Blocks many medications' absorption
Ezetimibe *Ezetimibe*	Binds to cholesterol and prevents its absorption (No dietary cholesterol)	Increased LDL receptor expression Clears LDL from circulation Terrible GI distress and foul-smelling stool
Fibrates *Fenofibrate* *Gemfibrozil*	Stimulate lipoprotein lipase, increasing deposition of triglycerides in organs	Makes serum triglycerides lower Makes organ triglycerides higher
Niacin *Niacin*	Inhibits hormone-sensitive lipase, decreasing the release of free fatty acids from adipose	Makes serum triglycerides lower Keeps adipose triglycerides higher Also increases HDL but induces diabetes and gout. Flushing treated with ASA
PCSK9 Inhibitors *Alirocumab* *Evolocumab*	PCSK9 degrades LDL receptors PCSK9 inhibitors prevent that degradation	Increased LDL receptor longevity Clears LDL from circulation Injectable monoclonal antibodies are used only as an adjunct to statins or where statins cannot be used.

Table 2.1: Summary Table
Rather than memorizing a laundry list of arrows for this cholesterol or that cholesterol, use this table to see why you should use statins and not the others. The intestinal blockers induce the same high-quality effects as statins, but with GI side effects. Fibrates and niacin just make the numbers look better. And the new guys, PCSK9 inhibitors, are probably good, too.